## REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not raise any new issue requiring further search and/or consideration because the amendments amplify issues previously discussed throughout prosecution, and places the application in better form for an appeal should an appeal be necessary.

As noted in the Office Action Summary, claims 27, 29-40, 45 and 47-53 are pending. Claims 29, 48, and 49 are amended herein to remove the term "unit". The Specification is amended herein to address formalities, such as the use of parentheses rather than brackets. Thus, no new matter is set forth by way of the present Amendment. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled by way of the present Amendment.

***Specification***

The Office requests that the Specification be amended to comply fully with 35 U.S.C. § 112, first paragraph. For example, the Office asserts that the use of brackets rather than parentheses, is confusing. The Specification is amended herein to replace brackets, as used with the sequence identifiers, with parentheses. By way of further explanation for the use of brackets, Applicants note that "RHHGP[G]" and "RHHGP-1" are not amino acid sequences, but rather symbols of peptides. Thus, the use of brackets in this context is appropriate, and should not be construed as a deletion in an amino acid sequence. (*See* page 21, lines 8-11 and page 23,

lines 20-22, of the present Specification). The Specification is also amended to address the other locations in the Specification which the Office objects to, as set forth on page 2 of the Office Action.

The Office further notes that the in the Sequence Listing filed June 7, 2002, SEQ ID NO:25 is given as "Arg His His Gly Pro Xaa", where Xaa=Gly instead of as "Arg His His Gly Pro Gly" (Office Action at page 3). Applicants respectfully request clarification from the Examiner regarding this issue, as Applicants believe that SEQ ID NO:25, as filed on June 7, 2002, complies fully with the requirements of 37 C.F.R. §§ 1.821-825.

The Office notes that the sequences of SEQ ID NO:25 and SEQ ID NO:8 are both described as "amino acid sequence containing a site cleaved by Kex2 Protease", but that neither sequence appears to contain such a site (Office Action at page 3). As noted in 37 C.F.R. § 1.823, Numeric Identifier <223> is for up to four lines of other relevant information. Applicants believe the current description is acceptable information for Numeric Identifier <223>. In addition, information regarding Kex2 enzyme cleavage may be found at, for example, page 17, lines 9-13, of the Specification. Should additional information be needed by the Examiner regarding this issue, clarification is respectfully requested.

Finally, Applicants note that the Specification as-filed does recite "glucagon-like peptide-1" as the full-spelling of "GLP-1", on page 2, lines 20-22, which is the first instance in the Specification of the abbreviation "GLP-1". However, in an effort to expedite prosecution in this matter, Applicants have amended the paragraph beginning at page 2, line 20, to read ("GLP-1") immediately following the first recitation of glucagon-like peptide-1.

***Objections to the claims***

With regard to previous amendments to the claims reciting "helper peptide unit", the Office asserts that the term "unit" is not present in the Specification (Office Action page 3). Without acquiescing in this objection, independent claims 29, 48, and 49 are amended herein to remove the term "unit"; instead reciting "a fusion protein comprising a protective peptide and the peptide of interest having a helper peptide added thereto". In addition, new claim 54 is added, reciting "fusion protein comprising, from the N-terminal to the C-terminal, a protective peptide, a helper peptide, and a peptide of interest", as suggested by the Examiner. As the term "unit" is no longer recited in the claims, Applicants request that the objection be withdrawn.

Regarding "GLP-1," (Office Action page 3) please refer to the final paragraph in the preceding "Specification" section.

***Rejection Under 35 U.S.C. § 112, First Paragraph***

Written Description

Claims 27, 29-40, 45 and 47-53 have been rejected under 35 U.S.C. § 112, first paragraph, as purportedly lacking written description. The Office asserts that the claims recite a genus of peptides of interest, a genus of helper peptides and a genus of protective peptides, and that these genera encompass an infinite number of peptides of any structure and from any source, as long as the isoelectric point of the fusion protein is between 8-12 (Office Action at page 4). Claims 38-40, 45, 50 and 51 are also rejected as directed to a peptide of interest, GLP-1 derivatives. The Office asserts that because the number of allowed substitutions, additions and/or

depletions is not limited, the GLP-1 derivative can have an amino acid sequence with an unknown homology to human GLP-1. Applicants respectfully traverse.

The subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. M.P.E.P. § 2163.02. The presently claimed invention is directed to the use of a fusion peptide containing two cleavage sites, which are cleaved with processing enzymes. However, Applicants submit that the Specification, in combination with what is known in the art, sufficiently describes the peptides of interest, helper peptides, and protective peptides. Applicants refer to the disclosure regarding the peptides of the present invention. Page 10, line 34 to page 11, line 27, recite specific peptides of interest, as well as properties to be desired in such peptides. Page 9, line 36 to page 10, line 33 recites specific helper peptides and describes in detail the properties of appropriate helper peptides, including specific guidance with regard to structure, length of sequence, isoelectric point, and acidity/alkalinity. Page 18, line 1 to page 19, line 27 discloses and lists protective peptides. Thus, not only does the Specification set forth specific peptides as used in the present invention, but methods of determining peptides not specifically listed are also provided.

With regard to the derivatives of GLP-1, Applicants submit that the amino acid sequence of GLP-1, 37 amino acid residues, is known. Thus, modification of the GLP-1 sequence by the skilled artisan to arrive at an appropriate derivative would be standard and is supported by the Specification, such that a GLP-1 derivative would not have an amino acid sequence with an unknown homology to human GLP-1. Furthermore, the Specification provides a lengthy list of derivatives of GLP-1, as well

as methods of determining appropriate derivatives. Page 2, line 20 to page 3, line 25 and page 11, line 28, through page 15, line 11 discuss in detail GLP-1 derivatives as well as providing detailed information with regard to amino acid substitutions.

In light of the above comments, Applicants submit that the scope of the present claims are sufficiently described in the Specification.

Enablement

Claims 27, 29-40, 45, and 47-53 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly lacking enablement. The Office admits that the application enables a process for making derivative of *human* GLP-1 using fusion proteins shown at Figures 7, and 11-13 and fusion proteins wherein a given GLP-1 derivative is substituted by any of the GLP-1 derivatives recited in the Specification. *See* Office Action at 6. However, the Office asserts that the Specification does not reasonably provide enablement for a process of making a peptide of any structure and/or function or GLP-1 derivative using other helper and protective peptides. Office Action at 6-7. Applicants respectfully traverse.

As stated in *Ex parte Forman* (230 U.S.P.Q. 546 (1986)) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As, the Office is aware, "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

To this end, Applicants submit that the presence of examples, guidance in the Specification, combined with what is known in the art, renders the claims enabled.

The Office specifically asserts that while the Specification teaches a method for making a highly purified GLP-1 derivative, it does not provide guidance as to a process for producing a highly purified peptide of any function or characteristics. Office Action at 6.

Applicants submit that the presently claimed process provides a method of industrial production of a peptide of interest derived from the physicochemical properties of the peptide of interest. Before the present invention, such production would result in problems such as yield, process control and cost. To address these problems, the present process includes a fusion peptide comprising a protective peptide, a helper peptide, and the peptide of interest. First the fusion peptide is cleaved at a first cleavage site to remove the protective peptide in order to obtain an intermediate fusion peptide comprising a peptide of interest and a helper peptide. Next, the intermediate fusion peptide is purified. The helper peptide is present to improve the properties of the intermediate fusion peptide and to place it in the most advantageous configuration for the purification process.

Thus, for example, the structure of the helper peptide depends on the structure of the peptide of interest. During the purification, it is very important to control coagulation and precipitation, which depend on the acidity and hydrophobicity of the protein to be purified. Therefore, if the peptide of interest is too acidic, the helper peptide should be basic, and vice versa. Similarly, if the peptide of interest is too hydrophobic, then the helper peptide should be hydrophilic. Applicants note that the calculation of acidity and hydrophobicity, and thus the ability to easily determine

the appropriate helper peptide, are readily available to the skilled artisan. For example, software such as ExPASy (http://kr.expasy.org/tools/pitool.html and http://kr.expasy.org/cgi-bin/protscale.pl) are well known and were readily available at the time the present invention was filed.

Applicants further submit that the skilled artisan would be able to determine the appropriate protective peptide without undue experimentation. Protective peptides, such as *E. coli* β-galactosidase, glutathione transferase, and maltose-binding protein, are well known in the art.

Thus, Applicants submit that the peptides of the present invention can be easily determined and designed based on the selected peptide of interest. Once the peptide of interest is determined, the appropriate helper peptide is the one that will produce the most ideal isoelectric point range for the prevention of coagulation (pI 8-12) in combination with the peptide of interest. For example, if the helper peptide must be acidic to counteract the basic nature of the peptide of interest, then the helper peptide should contain a large amount of acidic amino acids, such as aspartic acid or glutamic acid. If a basic helper peptide is desired, then basic amino acids, such as arginine and lysine, should be used.

In light of the above remarks, Applicants request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

## CONCLUSION

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

Respectfully submitted,
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